

## Case Report

# A Novel Mutation in Frabin (*FGD4*) Causing a Mild Phenotype of CMT4H in an Indian Patient

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**Abstract.** Charcot-Marie-Tooth disease 4H (CMT4H) is an autosomal recessive demyelinating form of CMT caused by *FGD4/FRABIN* mutations. CMT4H is characterized by early onset and slowly progressing motor and sensory deficits in the distal extremities, along with foot deformities. We describe a patient with CMT4H who presented with rapidly progressing flaccid quadriparesis during the postpartum period, which improved significantly with steroid therapy. Magnetic resonance imaging and ultrasonography demonstrated considerable nerve thickening with increased cross-sectional area in the peripheral nerves. A nerve biopsy revealed significant demyelination and myelin outfolding. This is the first report of an Indian patient with a novel homozygous nonsense c.1672C>T (p.Arg558Ter) mutation in the *FGD4* gene, expanding the mutational and phenotypic spectrum of this disease.

**Keywords:** Charcot-Marie-Tooth disease type 4H (CMT4H), *FGD4*, Indian, novel homozygous mutation, histopathology

## INTRODUCTION

Charcot-Marie-Tooth disease (CMT) also known as hereditary motor and sensory neuropathy (HMSN) is one of the most common inherited neurological disorders comprising a group of genetically

and phenotypically diverse conditions. It is caused by mutations in genes that encode proteins involved in the structure and function of either the peripheral nerve axon or the myelin sheath of nerves [1]. It occurs approximately with a frequency of 1 in every 2500 individuals [2]. It is clinically characterized by progressive motor and sensory deficits arising at distal extremities causing weakness, atrophy, depressed tendon reflexes, and hypoesthesia of feet and legs along with foot deformities such as pes cavus and pes planus [3]. Based on electrophysiological (nerve conduction studies) and histopathological findings, it

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is classified into demyelinating forms (NCV <38 m/s) such as CMT1 (autosomal dominant) and axonal forms (NCV >38 m/s) such as CMT2 (autosomal dominant or recessive) [3].

CMT4H is an autosomal recessive demyelinating form of CMT [4]. This type of CMT is characterized by an early age of onset, and slow progression, but is more severe than other phenotypes described. It is caused by mutations in the *FGD4* gene that encodes a protein called frabin, which serves as a GDP/GTP exchange protein for Rho GTPase Cdc42 (cell-division cycle 42), a small GTP binding protein family member that is involved in regulating the actin cytoskeleton-dependent cellular activities in Schwann cells [5, 6]. In 2005, Giovannoli et al. mapped this disease to a novel locus on chromosome 12p11.2- p13.1 in Lebanese and Algerian families affected with severe autosomal recessive CMT [7]. Later, in 2006, Delague et al., found mutations in *FGD4*, encoding frabin (FGD1-related F-actin binding protein) in the same patients [8].

This subtype of CMT is relatively uncommon, and there have been no reports of this type in an Indian patient [3, 4]. Here, we describe the first case of an Indian woman with CMT4H with a novel *FGD4* mutation, who presented to our tertiary care center with a mild phenotype and postpartum exacerbations by highlighting the clinical, radiological, histopathological and genetic findings.

## MATERIALS AND METHODS

### *Case description*

This report is a description of the clinical, radiological, histopathological and genetic mutation findings in a case of *FGD4*. Institutional ethics committee approval was obtained to collect all data from the medical records maintained at the hospital. The clinical details are written meticulously in the case records and all images were retrieved from the PACS system. The patient provided consent for the unmasking of the face.

### *Radioimaging*

Ultrasonography was performed using Philips Diagnostic scanner EPIQ 7 using an 8–15 MHz linear transducer. CSA (cross-sectional area) was measured at the median (wrist crease, mid-forearm- at the midpoint between the wrist crease and elbow crease, elbow -medial to the brachial artery), ulnar

(wrist crease, mid-forearm - at the midpoint between the medial epicondyle and ulnar styloid, elbow-at the ulnar groove). Upper limb nerves were studied with the patient in the supine position, and the arm abducted to 60° at the shoulder and forearm in the supine position. Power and color doppler modes were used. The inner border of the thin hyperechoic epineurial rim was traced using the trace function.

MRI (Magnetic Resonance Imaging) of the Brachial plexus was performed on 3T PHILIPS INGENIA scanner with the addition of a 3D NERVE VIEW sequence (TR/TE:2200/170 ms, TI:250 ms, acquisition voxelsize: 0.6 × 0.5 × 1.1 mm, Recon Voxel: 0.6 × 0.6 × 1.00 mm, Slice thickness: 1.1 mm). It employs a Motion-sensitive driven equilibrium (MSDE) PREPPED 3D sampling perfection with application optimized contrasts using different flip angle evolution (SPACE) scheme for short tau inversion recovery (STIR) contrast (3D NERVE VIEW SEQUENCE, PHILIPS) to achieve optimal MR neurography (MRN). 8-mm-thick slabs of Maximal Intensity Projection (MIP) were reconstructed from the 3D data set.

### *Mutational analysis*

Genetic testing was performed by whole exome sequencing (WES) using Exome Research Panel (Integrated DNA technologies, USA). DNA was extracted from whole blood samples collected from proband, unaffected sister and mother. Sequencing was performed on Illumina sequencing platform with a mean coverage of >50×. Raw sequences were aligned to human reference genome (GRCh37/hg19) using BWA program followed by variant identification using Picard and GATK version 3.6 [9, 10]. Variant annotation was performed using VEP program against the Ensembl release 87 human gene model [11]. Pathogenic / likely pathogenic variants are classified as per American College of Medical Genetics and Genomics (ACMG) criteria [12].

### *Histopathological examination*

The left superficial radial nerve biopsy was fixed in 2.5% glutaraldehyde. Paraffin embedded sections stained with hematoxylin and eosin, and resin embedded semithin sections stained with 1% toluidine blue were studied by light microscopy. Uranyl acetate and lead citrate stained ultrathin sections were subjected to electron microscopy.

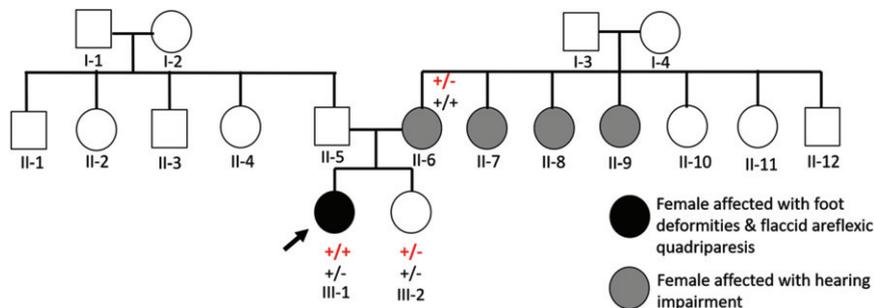
## CLINICAL PRESENTATION

The patient is a 23-year-old lady evaluated in February 2017 during her postpartum period. She presented at the emergency services with rapidly progressive flaccid quadriplegia. She was born by normal delivery as the first child of non-consanguineous parents. She had bilateral foot deformities (pes cavus and hammer toes) since early childhood. She first noticed bilateral limb weakness during the 7th month of gestation which continued during the postpartum period of the 1st pregnancy at 21 years of age. The weakness improved spontaneously over 5 months. During her second pregnancy at the age of 23 years, she similarly developed worsening of the existing limb weakness and could not rise from the floor. Post-delivery the weakness worsened rapidly and she had flaccid quadriplegia and was evaluated at the emergency services at the end of two months after delivery. She required one person's support to walk. At the end of 2 months of the onset, she developed distal weakness in all limbs in the form of finger and toe grip weakness. The patient was started on oral steroids (Prednisolone of 30 mg per day) and there was a significant improvement in distal muscle power and she attained independent ambulation. After six months of initial presentation, she

complained of squeezing pain in the right shoulder radiating to the hand which subsequently progressed to the other limb as well. The pain was worsened by shoulder movements and relieved by steroids and pain management with prednisolone (30 mg/day) and a combination of gabapentin and amitriptyline (300 mg/day).

The pedigree of the patient is shown in Fig. 1.1. The patient's mother was born deaf and dumb, and has bilateral profound hearing loss and speech impairment and further examination revealed short stubby fingers, high-arched feet, and coarse facies. A family history of deafness and speech impairment is present in three maternal aunts (Fig. 1.1). The patient's father has hand and foot deformities since adolescence, but there is no definite or minimal progressive illness and capable of doing all activities of daily living (Fig. 1.2). The cranial nerves and proximal muscles were normal. Severe weakness of the small muscles of hands and feet present. Tendon reflexes were absent. Pain and touch and temperature sensations were impaired in glove and stocking distribution. He refused further evaluation. The younger sister of the proband has normal development and showed no signs of neuropathy.

*Clinical examination* at 23 years of age revealed a short-statured woman with bilateral hammer toes,



### FGD4

chr12:32778624C>T; c.1672C>T; p.Arg558Ter; ENST00000427716

The reference allele "C" is marked as "-" in the pedigree; The alternate allele "T" is marked as "+" in the pedigree individuals; individuals marked as "+/" are heterozygous for the variant

### DFNB59

chr2:179325958A>T; c.1016A>T; p.His339Leu; ENST00000409117

The reference allele "A" is marked as "-" in the pedigree; The alternate allele "T" is marked as "+" in the pedigree individuals; individuals marked as "+/" are heterozygous for the variant

Fig. 1.1. The pedigree of the present proband with the FGD4 gene mutation is illustrated.



Fig. 1.2. Father aged 64 years developed hand and foot deformities from adolescence which has been minimally to non-progressive. The figures show evidence of severe wasting of the hands and feet with deformities.

Table 1  
Nerve conduction studies

CMAP Nerve	DL (ms)	Amplitude ( $\mu$ V)	Distance (distal/proximal) (mm)	NCV (m/s)
Rt. Median at wrist	17.10	273	60/220	7.0
Rt. Median at elbow	45.10	90	200	NR
Ulnar	NR	NR	NR	NR
Common peroneal	NR	NR	NR	NR

CMAP, Compound motor action potential; DL, Distal latency; ms, milliseconds;  $\mu$ V, microvolts; mm, millimeter; NCV, Nerve conduction velocity; m/s, meters per second; NR, Non-recordable. SNAPs were not elicitable in the median, ulnar, and sural nerves.

ankle contractures, and mild weakness of facial muscles. Weakness of proximal upper and lower limbs (MRC [Medical Research Council] scale = 3) along with mild weakness in the intrinsic hand and foot muscles (MRC scale = 4), global areflexia, loss of superficial sensation (touch, pain, and temperature) in lower limbs in stocking distribution; impaired vibration sense in hands and toes were noted. At the last follow-up, i.e. six years (2023) after the initial presentation, her symptoms remain stable except for occasional pain and moderate proximal limb girdle weakness.

*Investigations* showed normal creatine kinase level (CK). Nerve conduction studies demonstrated absent CMAPs (compound muscle action potentials) in bilateral ulnar and common peroneal nerves; increased distal latencies and amplitudes in the right median nerve (Table 1). SNAPs (sensory nerve action potentials) could not be elicited in upper and lower limb nerves.

*Ultrasound* of peripheral nerves showed the CSA of median and ulnar nerves were increased throughout their course (Fig. 2). MRI of the Brachial plexus showed symmetric thickening with T2 hyperintense

signal of the roots, trunks, divisions, and cords of bilateral brachial plexus (Fig. 3).

Exome sequencing revealed a homozygous non-sense variation c.1672C>T (p.Arg558Ter) affecting exon 14 of the *FGD4* gene (Refseq transcript ID: NM.139241.3) in the proband resulting in premature truncation of the protein with loss of distal FYVE and 2nd Pleckstrin homology (PH2) domains. The p.Arg558Ter has been reported as pathogenic in Clinvar (Clinvar ID: 1402656). On segregation analysis, the observed variant was detected in a heterozygous state in the mother and sister who did not have a CMT phenotype. A novel homozygous missense variant, c.1016A>T (p.His339Leu) in exon 7 of the *DFNB59* (*PJVK*) gene (Refseq ID: NM.001042702.5) was found in the proband's mother affected with hearing loss, which segregated as, heterozygous in the proband and the unaffected sister.

*Histopathology* showed significant nerve fiber loss, several thinly myelinated fibers, and poorly formed onion bulbs (concentric Schwann cell hyperplasia) indicating a chronic demyelinating process. Several fibers showed abnormal focally folded myelin consisting of thick myelin folds forming redundant outfoldings and inpouchings (Fig. 4).

## DISCUSSION

CMT4 is an autosomal recessive form of CMT and mutation in the *FGD4* gene is implicated as the cause of this disease. *FGD4* encodes a protein called frabin, which belongs to the family of Rho guanine nucleotide exchange factors (RhoGEFs) that activate Rho GTPases, such as Cdc42 and Rac1, by catalyzing the exchange of GDP for GTP [5, 7, 8, 13]. RhoGTPases are key regulators of the actin cytoskeleton, which is essential for various cellular processes, such

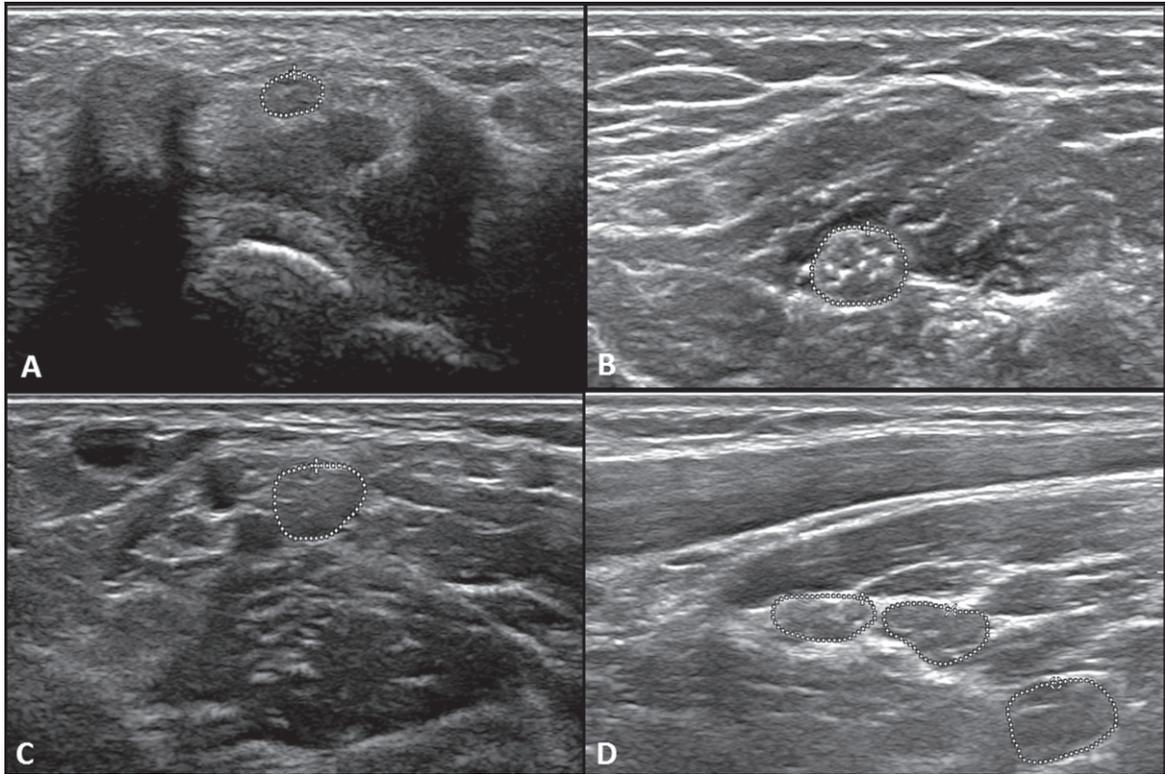


Fig. 2. Ultrasound cross-section images of the median and ulnar nerves. Fig. 2.1 (a) Right Median nerve at the wrist (area = 5.9 mm<sup>2</sup>), (b) Right Median nerve at mid-forearm between the flexor digitorum superficialis and flexor digitorum profundus (area = 17.8 mm<sup>2</sup>), (c) Right Median nerve at the elbow medial to the brachial artery (area = 15.6 mm<sup>2</sup>), (d) Right Brachial plexus upper (area = 14.2 mm<sup>2</sup>), middle (area = 16.9 mm<sup>2</sup>), and lower trunk (area = 25.7 mm<sup>2</sup>).

as cell shape, migration, polarity, and adhesion [14]. Frabin is mainly expressed in the nervous system and plays a role in neuronal development and function, such as axon guidance, dendritic spine formation, synaptic plasticity, and neurotransmitter release [15]. Mutations in FGD4 cause CMT4H by disrupting the normal function of frabin and impairing the signaling pathways that regulate the actin cytoskeleton and myelination in Schwann cells [16].

Table 2 presents a summary of Clinical, genetic and histopathological details of previously reported cases. Horn et al., found that frabin plays an important role in myelin development as well as maintenance [6]. They found that disruption in this gene and the subsequent protein cascade can cause myelin abnormalities as soon as the fifth day of postnatal life in animal models. This explains the early onset of neurological symptoms in our patient similar to the other reported studies [16–19]. Our patient had foot deformities since childhood but the other typical neurological features didn't develop until later in adulthood. The proband had both motor and

sensory involvement which was demonstrated by the electrophysiological studies. Usually, CMT4H is characterized by distal weakness at the onset of symptoms, but in contrast, our patient presented with proximo-distal weakness in the postpartum period mimicking an inflammatory demyelinating process [17, 20]. Interestingly, our patient developed these symptoms in the postpartum period of both of her pregnancies. The reason for this phenomenon is unclear, but it may be related to hormonal or immunological changes that occur during pregnancy and postpartum. Previous studies have suggested that estrogen may have a protective effect on peripheral nerve function and myelination, while progesterone may have a detrimental effect [21, 22]. Moreover, pregnancy and postpartum may alter the immune system and trigger autoimmune reactions that could affect nerve integrity [23]. Further investigations are needed to elucidate the role of hormonal and immunological factors in modulating the disease course of CMT4H. Moreover, the present proband had a mild to moderate clinical course as opposed to the first

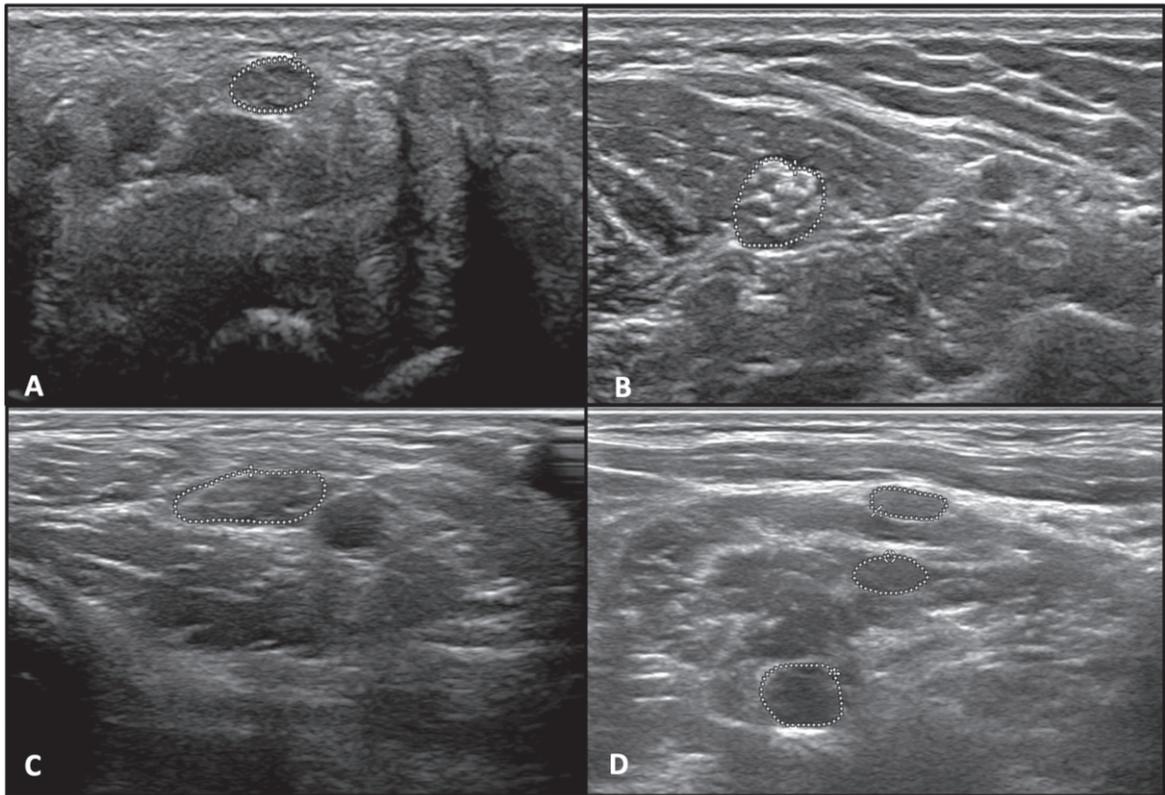


Fig. 2.2. (a) Left Median nerve at the wrist (area =  $8.6 \text{ mm}^2$ ), (b) left Median nerve at mid-forearm between the flexor digitorum superficialis and flexor digitorum profundus (area =  $18.2 \text{ mm}^2$ ), (c) Left Median nerve at the elbow medial to the brachial artery (area =  $20.8 \text{ mm}^2$ ), (d) Left Brachial plexus upper (area =  $16.1 \text{ mm}^2$ ), middle (area =  $6.8 \text{ mm}^2$ ), and lower trunk (area =  $8.0 \text{ mm}^2$ ).

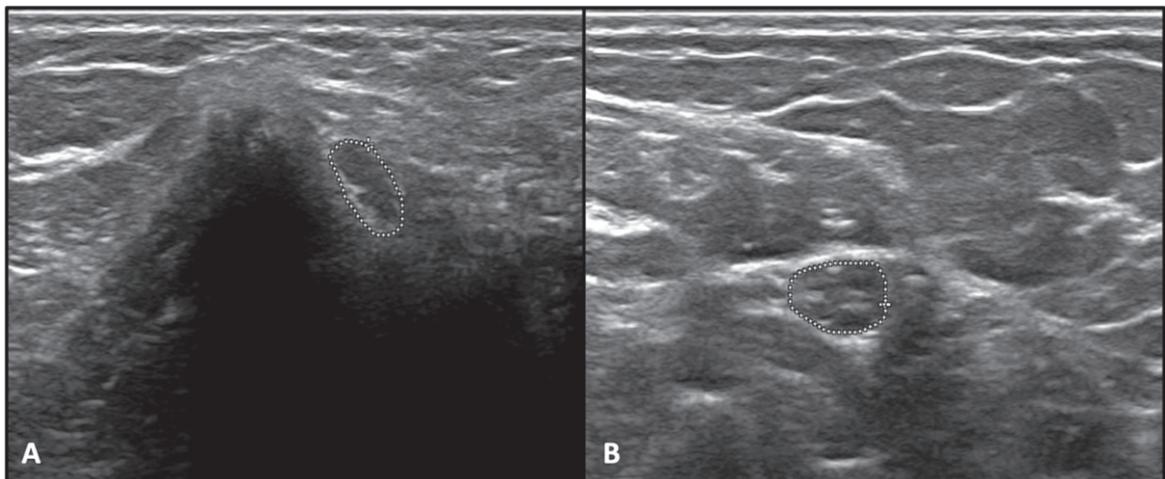


Fig. 2.3. (a) Right Ulnar nerve at mid arm (area =  $13.9 \text{ mm}^2$ ), (b) Right Ulnar nerve at the elbow medial to the brachial artery (area =  $17.4 \text{ mm}^2$ ).

reported cases where they had severe neurological features with deformities, and for this reason, it was thought to be a more severe form compared to other autosomal recessive CMTs [7, 8, 24]. Therefore,

our report further widens the clinical spectrum of CMT4H.

Limited studies are available on nerve ultrasound in inherited neuropathies. In CMT1A, and MPZ-

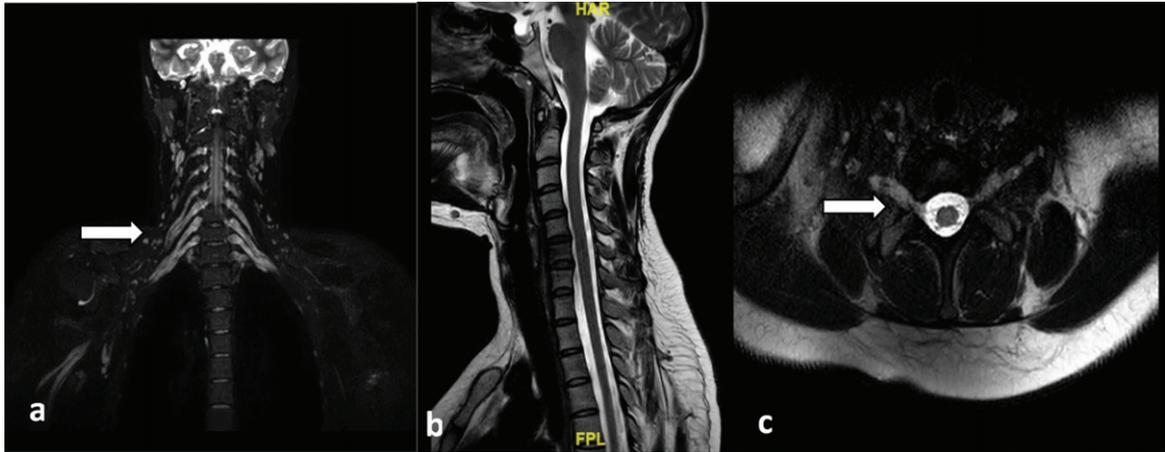


Fig. 3. MRI of the Brachial plexus. (a,c) Near symmetric thickening with T2 hyperintense signal of the roots, trunks, divisions, and cords of the bilateral brachial plexii (arrows), (b) T2W image of the sagittal section showing normal spinal cord. (MRI, Magnetic resonance imaging).

MPZ-associated CMT, uniformly increased CSAs were found whereas, it was not increased in CMT due to NEFL-associated CMT [25]. Focal enlargements have been described in HNPP (Hereditary neuropathy with pressure palsies) [26]. The ultrasonography of our patient showed that the CSAs of median and ulnar nerves were increased throughout their course, suggesting diffuse nerve enlargement. The normal values for median and ulnar nerve CSAs vary depending on the anatomical site, age, sex, height, and weight of the subjects [27]. According to a recent study by Sindhu et al., the mean CSAs of median and ulnar nerves in the Indian population are  $7.42 \pm 1.39$  mm and  $4.43 \pm 0.79$  mm at the wrist,  $5.1 \pm 0.91$  mm and  $4.52 \pm 0.83$  mm at the forearm,  $7.77 \pm 1.6$  mm and  $5.64 \pm 1.26$  mm at the elbow, and  $5.9 \pm 0.9$  mm and  $4.3 \pm 0.5$  mm at the upper arm, respectively [27]. We could not find any previous studies on the USG of nerves in CMT4H.

Whole-exome analysis by next-generation sequencing has been successful in determining the genes causing various CMT types [28, 29]. Over 30 *FGD4* mutations causing CMT4H have been reported until now that resulted in truncated or absent protein (missense, nonsense, frameshift, or splicing mutations) [8, 17, 20, 30]. We identified a homozygous nonsense mutation in *FGD4*, c.1672C>T (p.Arg558Ter) that has not been published in literature before but classified in Clinvar as pathogenic based on a single submission (<https://www.ncbi.nlm.nih.gov/clinvar/variation/1402656/>). Recessive loss of function mutations including nonsense and frameshift variants in *FGD4* have been previously reported in CMT4H patients [16, 30]. Such nonsense

and frameshift variants are often expected to result in nonsense mediated decay (NMD), a cellular surveillance mechanism that degrades mRNAs leading to complete loss of protein especially when premature termination codon (PTC) is located significantly upstream to the last exon [31]. The current variant p.Arg558Ter introducing PTC in exon 14 out of 17 exons of *FGD4* is thus expected to lead to complete loss of protein due to NMD. Truncating mutations distal to the current variant in *FGD4* have been previously reported to cause a severe phenotype [16]. However, Houlden et al reported a milder CMT4H phenotype in a patient with a proximal nonsense mutation p.Arg275Ter which was shown to escape NMD as evidenced by the presence of residual mRNA expression indicating a non-correlation between location of truncation and severity of phenotype in *FGD4* patients [20]. Our findings further support this hypothesis and indicate that NMD efficiency may be influenced by factors other than the location of the mutation relative to the last exon-exon junction. For instance, NMD can be modulated by cellular stress, microenvironmental cues, and alternative splicing events [31, 32]. Further studies are needed to elucidate the exact molecular mechanisms underlying NMD regulation and its impact on *FGD4* expression and function.

On segregation analysis, we found that the patient's mother and sister were heterozygous carriers of the mutation. Since the father was not tested further, it is difficult to determine whether his hand and foot deformities can be attributed to *FGD4* or if other causative variants were present. The clinical manifestations of CMT4H are highly variable, even among

Table 2  
Clinical, genetic and histopathological features of previously reported cases

Parameter	Current report	Delague et al. 2007 [8]	Houlden et al. 2009 [20]	Fabrizi et al. 2009 [17]	Baudot et al. 2012 [38]	Boubaker et al. 2013 [24]	Arai et al. [18]	Hyun et al. 2015 [39]	Zis et al. 2017 [40]	Kondo et al. [19]	Argente et al. [30]	Ouyang et al. [41]	Aoki et al. 2021 [42]	Zhan et al. 2021 [43]
Origin	Indian	Lebanese and Algerian	Irish	Italian	Lebanese and Algerian	Tunisian	Japanese	Korean	Caucasian	Japanese	Spanish	Chinese	Japanese	Chinese
Age at onset (years)	Childhood	1 to 2	Childhood	<1 year	3 to 5	3	4	6 to 8	8	15	11 to 19	8	7	11
Sex	F	M	F	F	F and M	F:M = 2:1	F	M	F	M	M, F	F	F, M (siblings)	M
Consanguinity	Sporadic	Consanguineous	Consanguineous	Consanguineous	Consanguineous	Consanguineous	Sporadic	Sporadic	Sporadic	Consanguineous	Sporadic	Consanguineous	Consanguineous	Sporadic
Motor symptoms	B/L proximal upper and lower limb weakness	Delayed motor milestones and gait unsteadiness with scoliosis	Distal muscle weakness and wasting	Distal muscle weakness and wasting in lower limbs	Distal muscle weakness and wasting	Wasting of upper and lower limb	Distal left leg weakness	Distal muscle weakness; proximal lower limb weakness	Distal muscle weakness of upper limbs	Distal muscle weakness and wasting	Reduced heel walking	Foot deformities, facial weakness	Distal muscle weakness and wasting	Toe walking, gait disturbance, falls.
Sensory symptoms	Sensory loss in lower limbs	Stocking type hypoesthesia	Distal hypoesthesia	Distal hypoesthesia	–	Distal hypoesthesia	Glove and stocking-type sensory loss in both legs	Sensory loss in lower limbs	Severe sensory loss in upper and lower limbs	Sensory loss in upper and lower limbs	None	Numbness of limbs	Distal hypoesthesia	None
Scoliosis	No	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes	No	No	Yes	No
Foot deformities	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Mutation	c.1672C > T p.Arg558Ter Nonsense	c.893 T > G p.Met298fs*8; c.893 T > C p.Met298Thr Missense, Splicing	c.823 C>T p.Arg275 Nonsense	c.1762–2 A>G p.Tyr587fs*14 Splicing	c.1698 G > A p.Met566Ile; c.1325 G > A p.Arg442 His Missense	c.514_515insG p.Ala172 Glyfs*7 insertion	c.8371G > A p.Glu280 Lysfs*23 Splicing	c.1512-2A > C (p.Arg468Gln); c.2043 + 1G > A (p.Met345Thr) Missense	c.1192-48_1233del p.(?); c.1304_1305 delins AA p(Arg435Gln) Frameshift, Missense	c.724C>T (p.Arg242X) Splicing	c.514delG p.Ala172 Glnfs*28; c.2211dupA p.Ala738 Serfs*5 Frameshift	c.1303C>T (p.R435W) Missense	c.1730G > A (p.Arg577Gln) Missense	c.1688C > A (p.T563K) and c.1951C>T (p.Q651X) Nonsense
Nerve biopsy	Demyelination with onion bulbs and myelin outfoldings	Demyelination with onion bulbs and myelin outfoldings	Not done	Demyelination with onion bulbs and myelin outfoldings	Not done	Demyelination with onion bulbs and myelin outfoldings	Demyelination with onion bulbs and myelin outfoldings	Demyelination with onion bulbs and myelin outfoldings	Not done	Not done	Not done	Not done	Demyelination with myelin outfoldings	Demyelination with myelin outfoldings

(M, Male; F, Female).

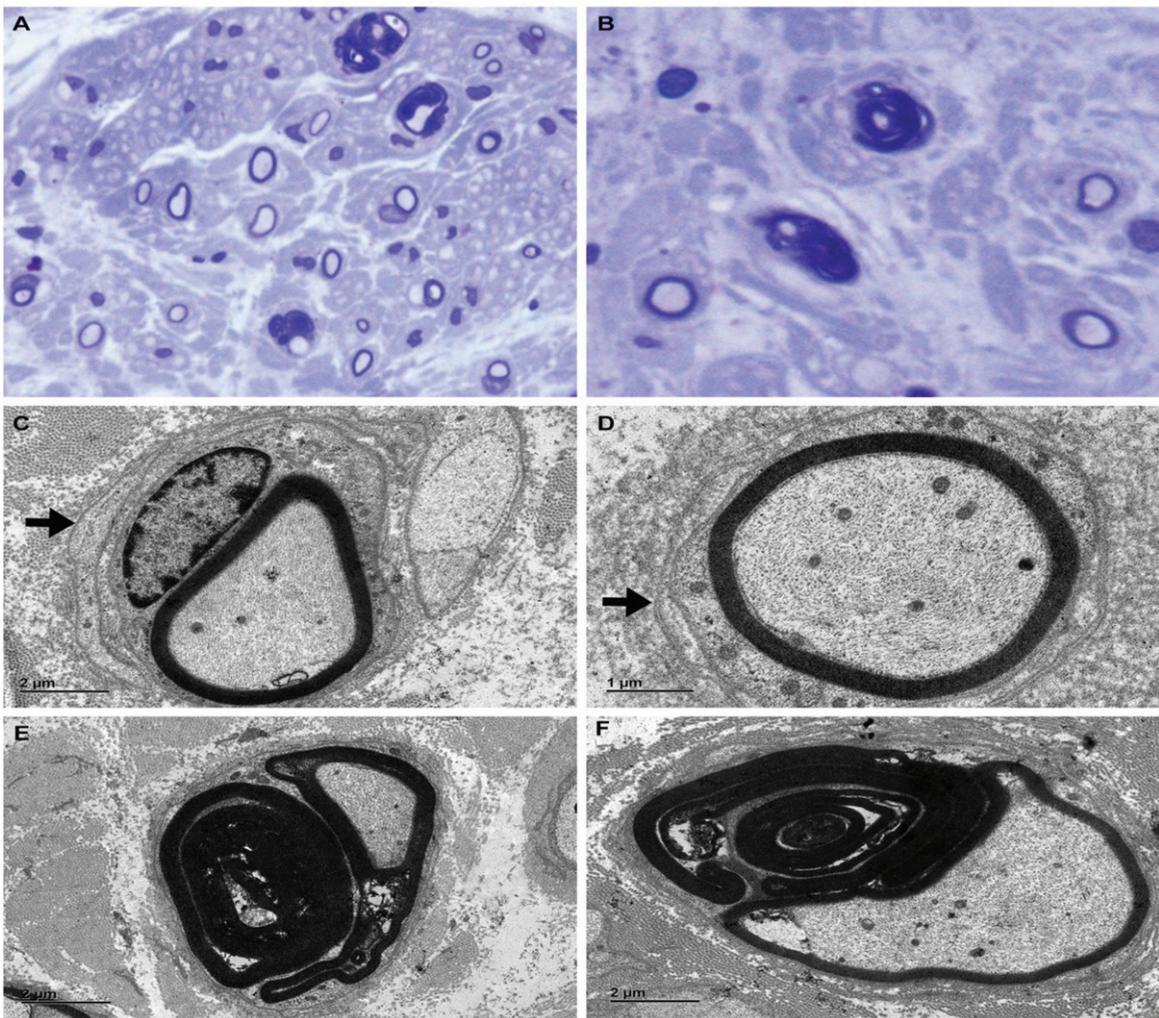


Fig. 4. Nerve biopsy: (A) and (B) Semithin sections of resin embedded tissue stained with toluidine blue show severe and fairly uniform depletion of myelinated fibers, thin myelin sheaths, occasional onion bulbs, and fibers with abnormal myelin folds (A  $\times 200$ , B  $\times 400$ ). (C) and (D) Electron micrography- Ultrathin sections stained with uranyl acetate and lead citrate reveal thinly myelinated fibers with Schwann cell lamellae (arrow) indicating early onion bulb formation [C  $\times 2000$ ; D,  $\times 4000$ ]. (E) and (F) Fibers with numerous thick abnormal myelin folds forming redundant outpouchings and infoldings [E & F,  $\times 2000$ ].

individuals with the same mutation [17]. Some factors that may contribute to this variability are the quality of the genotype, such as the presence of modifier genes or the epigenetic modification, such as the methylation status or alternative splicing of *FGD4*; the environmental influence, such as exposure to toxins or infections that may affect nerve function; and the mosaicism, such as the presence of somatic or germline mutations that may alter the expression or activity of *FGD4* [7, 33].

The exome analysis also showed a homozygous *DFNB59* variant c.1016A>T (p.His339Leu) in the proband's mother who has profound hearing loss

with speech impairment since childhood, but further testing was not done. Biallelic mutations in *DFNB59* or *pejvakin*, have been reported in patients with autosomal recessive non-syndromic hearing loss [34]. The onset of *DFNB59*-associated hearing loss is often prelingual in childhood with severity ranging from moderate to profound impairment [35]. In the present family, a history of hearing loss has been reported in maternal family (Fig. 1.1). However, the proband and unaffected sister carried only a heterozygous *DFNB59* c.1016A>T variant and did not have any hearing impairment. Furthermore, other maternal family members with hearing loss were

unavailable for evaluation and performing a segregation study. Based on the genotypes observed and segregation of both variants, we presume that the phenotypes in the proband and mother are unrelated and can be explained by *FGD4* and *DFNB59* mutations respectively.

Superficial Radial nerve biopsy in our patient displayed prominent demyelination and abnormal focally folded myelin. Myelin outfolding is the characteristic feature of this disease and has been reported previously in other studies of CMT4H [7, 8, 16, 17]. The formation and preservation of myelin structure are dependent on cdc42 signaling in the Schwann cells of peripheral nerves. As *FGD4* gene mutations disrupt this signaling pathway, these abnormal myelin outfoldings develop [36]. This pathological finding is also detected in other CMT4 subtypes such as CMT4B1 and CMT4B2 caused by *MTMR* and *SBF2* mutations respectively [36, 37].

To conclude, we report a novel mutation in the *FGD4* gene for the first time in an Indian patient. Our patient had milder features compared to previously reported studies broadening the CMT4 phenotype. The postpartum worsening of weakness in the form of flaccid areflexic quadriparesis significantly improved with steroid therapy, which is an interesting observation. The current report expands the phenotypic and genotypic spectrum of CMT4H caused by *FGD4* mutations.

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## CONFLICTS OF INTEREST

Authors do not have any conflict of interests.

## DISCLOSURES

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## DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available from the corresponding author upon reasonable request.

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